APPENDIX II

Atty. Dkt. No. 027668-0108

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Fred H. MILLER

Title: **MULTI-PHASE, MULTI-COMPARTMENT CAPSULAR DELIVERY APPARATUS AND METHODS FOR USING SAME**

Appl. No.: 10/804,576

Filing Date: 3/19/2004

Examiner: Aradhana Sasan

Art Unit: 1609

Confirmation Number: 7069

DECLARATION OF CAREY BOTTOM

I, **Carey Bottom**, a citizen of the United States of America and resident of the state of Indiana, U.S.A., declare and state as follows:

1. I possess expertise in the field of drug encapsulation (see curriculum vitae, appended). Thus, from February of 2003 to April of 2006, I was the Executive Vice President for Business Development & Technical Affairs at Qualicaps, Inc., the second largest producer of two-piece hard gelatin capsules worldwide. I am author of a number of publications that relate to pharmaceutical-grade ingestible capsules and, more generally, to barriers for separating chemicals/pharmaceuticals. In 1998, when I was a senior V.P. at Banner Pharmacaps, I received a citation from the U.S. Food and Drug Administration for my efforts, in conjunction with R.P. Schrer, then the world's largest soft gelatin capsule manufacturer in the world, to resolve product quality issues related to dissolution failures for gelatin capsule drug products.

2. From time to time, I act as a consultant to the pharmaceutical industry. In relation to this declaration, I am a paid consultant to Foley and Lardner, LLP.

3. International patent application WO 01/03676 ("PCT '676"), which I have reviewed, lists BioProgress Technology International, Inc. ("BioProgress") as

applicant/assignee. From September of 2002 to January of 2003, I was President of BioProgress Technology, Inc., having full business and technical responsibility for that U.S. subsidiary of BioProgress. From September of 2001 to January of 2003, I was a member of the Board of Directors of BioProgress, and an executive director after September, 2002.

4. I understand that PCT '676 is cited to substantiate a rejection of claims in the captioned patent application ("the subject application"). I am familiar with the technology described in PCT '676 and, by virtue of my position at BioProgress, I was privy to the thinking of the inventors named in PCT '676 ("the named inventors") about that technology. In particular, I knew the named inventors personally and discussed the technology with them.

5. I understand that the subject application claims priority to earlier applications filed in February, 2003, and I have been advised by Foley and Lardner, LLP, to direct my comments towards the timeframe up to and including February, 2003.

6. I have read PCT '676 and that portion of an Office Action dated January 17, 2008, detailing the aforementioned rejection of claims in the subject application. Thus, I understand that the U.S. Patent and Trademark Office (PTO) is asserting that it would have been obvious, *circa* February of 2003, to modify the teachings of PCT '676 to arrive at the subject matter of the rejected claims.

7. I am informed that certain claims, appended to this declaration, are or will be presented in the subject application, and that those claims recite a multi-compartment capsule that is a "hard shell" capsule. In particular, the presented claims are directed to what I denote as a hard shell, bi-phasic, multi-ingredient, multi-compartment capsule. By this last characterization, I intend to denote a capsule that presents ingredients in a plurality of the compartments, which ingredients differ, one from the other, in terms of physical phase.

8. The PTO asserts, I understand, that PCT '676 teaches a bi-phasic, multi-ingredient, multi-compartment capsule.

9. Based on a thorough review of PCT '676, it is my opinion that PCT '676 does not disclose or suggest that its teachings may be implemented in a hard shell capsule, which fact delineates a difference separating the teachings of PCT '676 from claims of the subject application that recite a hard shell capsule.

10. In view of the foregoing, I address my further comments here to the hypothetical modification of PCT '676 that the PTO may propound to obtain a hard shell, bi-phasic, multi-

ingredient, multi-compartment capsule according to the aforementioned claims ("the claimed capsule").

12. As of February, 2003, to the best of my knowledge no one in the drug encapsulation community had bridged the difference identified in paragraph 9 above, despite ample motivation to have done so. Indeed, there were reasons widely recognized in the drug encapsulation community for not modifying PCT '676 to obtain a hard shell capsule with the above-mentioned features.

13. A septum element, represented as "septum 16" in Figure 1 of PCT '676, is central to the disclosures in that document of a bi-phasic, multi-ingredient, multi compartment capsule. Thus, each embodiment of such a capsule in PCT '676 incorporates a "median dividing wall of septum 16" (see: Abstract; page 2, 5th paragraph; page 3, second paragraph; page 5, 5th paragraph; page 7, last paragraph - page 8, 5th paragraph; pages 9 - 13).

14. BioProgress had evolved the septum concept, as described in PCT '676, with the hope that it would be a significant advance in the drug encapsulation arts. Without this hope and the underlying development, BioProgress would not have pursued any multi-compartment capsule, including one with the bi-phasic and multi-ingredient features the PCT '676 details, e.g., at pages 7-13.

15. Critical to the aforementioned septum concept at BioProgress was the company's parallel development of a "pre-dried film." BioProgress came up with pre-dried film as a substitute for gelatin capsules, because gelatin, a byproduct of cattle processing, had taken on a negative connotation by virtue of concerns over bovine spongiform encephalopathy ("mad cow disease"). Indeed, PCT '676 states that the "capsule materials also have the advantage compared with gelatin of being non-animal derived, and so having no possibility of transmitting animal-related diseases such as" BSE (PCT '676, page 3, first paragraph).

16. Thus, it was always BioProgress' intention to use pre-dried film to produce capsules having a septum. Without the development of the pre-dried film, BioProgress in fact would not have developed a capsule including a septum as of February 2003, and thus would not have developed the bi-phasic, multi-ingredient, multi-compartment capsule described in PCT '676. BioProgress likewise considered the development of pre-dried film to be a significant step forward vis-à-vis drug encapsulation systems, including the preexisting hard shell capsule technology.

17. Inside and outside of BioProgress, there was widespread recognition that the pre-dried film development had spawned the embodiments described in PCT '676, including the bi-phasic, multi-ingredient, multi-compartment capsule. By the same token, the impression was widely entertained in the drug encapsulation community that the pre-dried film developed by BioProgress was unique to and necessary for a capsule with a septum, pursuant to PCT '676. One reason for this impression was the fact that the pre-dried film had a modicum of structural stability, prior to its use in capsule fabrication, and could readily receive an adhesive while remaining very pliable. This allowed for the use of capsule-forming machines that molded the capsule portions into form, prior to drug filling and compartment closure.

18. It is apparent from PCT '676 that the pre-dried film from which the described capsule is made also forms the septum in question; hence, that the pre-dried film is a prerequisite for the septum. For example, Figure 2 of PCT '676 shows that septum wall 16 is simply a flat portion of the pre-dried film from which the entire capsule is made. As Figure 2 demonstrates, the septum actually is an adjacent wall of two separate sub-capsules, made from the pre-dried film. Thus, the capsules of PCT '676 are composed essentially of two separate capsules, adhesively retained together, and the septum is a wall shared between them, in the fashion of the shared wall in a duplex home.

19. It was common knowledge in the drug encapsulation community that capsules made from the pre-dried film, as developed by BioProgress, were not hard shell capsules but, in fact, were the antithesis of such capsules in many respects.

20. BioProgress conceived of the pre-dried film in the mid-1990's. By contrast, hard shell capsules have been widely available since at least the 1930's, and hard shell capsule technology was well-known in the drug encapsulation industry. As of February, 2003, the view was widespread, within and outside of BioProgress, that the hard shell capsule format was unsuited and inadequate for producing a capsule with a septum, in accordance with PCT '676.

21. The machinery and manufacturing methodology that PCT '676 discloses for producing a capsule with a septum are directed entirely to using the pre-dried film. Indeed, as Figure 2 of PCT '676 shows, the described capsules and constituent septum are both formed from a ribbon of pre-dried film. Conversely, the teachings in PCT '676 regarding

manufacturing a capsule with a septum bear no relation to and, indeed, were seen as diametrically opposed to the manufacture of a hard shell capsule.

22. During my tenure with BioProgress, company management deemed the identification of new drug encapsulation systems as critical to financial success of the company. Accordingly, BioProgress employees, including the named inventors of PCT '676 and myself, had every incentive to develop new technologies in this regard. As of February of 2003, moreover, BioProgress was better positioned than any other company to modify and to identify modifications to the technology described in PCT '676; this, because BioProgress was developer of that technology and had undertaken to refine it, albeit without ever identifying any modification of the technology that implicated a hard shell capsule. Yet, to my knowledge, no one within BioProgress ever thought to modify the technology described in PCT '676 for use with hard shell capsules.

23. I am informed that PCT '676 was published in January, 2001. The period between January of 2001 and February, 2003, was a time of aggressive development in new capsule delivery systems. Yet, to the best of my knowledge, there was no public disclosure before or during this period of a hard shell capsule that reflected or embodied a modification the PCT '676 teachings, discussed above.

24. As of February, 2003, BioProgress had encountered difficulty in practical implementation of the technology described in PCT '676. One difficulty involved obtaining a sufficiently sealed capsule compartment. BioProgress identified this difficulty to be a direct result of the material properties of the pre-dried film. That is, BioProgress had difficulty utilizing the pre-dried film, and others would have had the same difficulty, when practicing the teachings of PCT '676. Pre-dried film was the underlying technological development upon which the teachings in PCT '676 were founded. Had they not recognized them beforehand, individuals in the field who attempted to practice the teachings of PCT '676 immediately would have encountered difficulties in sealing the capsule adequately.

25. The difficulties encountered by BioProgress in obtaining sufficiently sealed capsule compartments dissuaded BioProgress from attempting actually to manufacture a prototype capsule with a liquid component, such components being considered almost certain to escape from an inadequately sealed capsule. Thus, as of February, 2003, BioProgress had not produced a capsule that was characterized by bi-phasic ingredients and that otherwise

embodied the technology described in PCT '676. To the best of my knowledge, the same was true for other companies in the drug encapsulation field then.

26. Also in this timeframe, as I recall, capsules made with the pre-dried film had a tendency to fall apart within two months, or even a shorter time span, when subjected to the requisite storage temperature of 40° C over that period. Storage is an important feature in the drug encapsulation arts, and this tendency was recognized as unacceptable by BioProgress.

27. Because of the problems with sealing the capsules and the tendency of the capsules to fall apart, BioProgress also recognized that, in view of the state of the art as of February, 2003, capsules manufactured according to the teachings of PCT '676 would present serious efficacy problems. This recognition was common in the industry, moreover, given the likelihood that the ingredients would leak from the capsule, rendering uncertain the dosage of the ingredients (i.e., the amount of the ingredients delivered upon human consumption).

28. In the context of incompatible drug ingredients, because of the problems with sealing the capsules and the tendency of the capsules to fall apart, BioProgress further recognized that capsules manufactured according to the teachings of PCT '676 likely would be unsuitable for human consumption, and others in the industry would have agreed, because of the likelihood that incompatible drugs could come into contact with one another.

29. I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: April 25, 2008 Name: Carey Bottom

Carey Bottom, Ph.D

APPENDIX A

CAREY B. BOTTOM, Ph.D.

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SUMMARY

Experienced leader with broad background in pharmaceutical analysis, formulation development, preclinical studies, compound development, quality control, regulatory affairs, business development and corporate management. Successful history in project and people management. Proven ability to integrate and manage for success across disciplines.

OBJECTIVE

---To lead, direct and instill entrepreneurial spirit across a multi-discipline organization engaged in the development, approval and marketing of quality, cost-effective health and pharmaceutical products.

EDUCATION

Ph.D., Chemistry, University of Missouri-Rolla, 1979
M.S., Chemistry, University of Missouri-Rolla, 1975
B.S., Chemistry, University of Missouri-Rolla, 1972

AWARDS & HONORS

Phi Kappa Phi
Professional Degree, Chemistry, University of Missouri-Rolla, 1996
Distinguished Alumni Award, MSM/UMR Chemistry Department, 1998
FDA Commissioner's Special Citation, Gelatin Capsule Working Group, 1998

EXPERIENCE

Qualicaps, Inc., Whitsett, NC

Executive Vice President, Business Development & Technical Affairs (February, 2003 – April 2006)
Responsible for technical, quality, regulatory and new business development disciplines in the US. The company is the second largest producer of 2-piece hard gelatin capsules worldwide. Product quality and technology lacked competitiveness and as a consequence I have introduced the Quality Initiative Program (QIP) focused on assessment and improvement of manufacturing methods and quality systems. This has lead to new business with multi-national

pharmaceutical companies. Non-gelatin, hypromellose capsules have been introduced to US pharmaceutical companies and is receiving considerable interest for NCE's under development.

BioProgress Technology, Inc., Atlanta, GA

President (September, 2002 – January, 2003)
-Appointed to the position after serving on the Board as a non-executive Director and consultant. Full business and technical responsibility for the US subsidiary of BioProgress Technology International, Inc. BioProgress has a strong IP position in polymer film and engineering technology for a variety of applications to include medical devices, oral delivery systems, personal care and household products and numerous other applications. Business emphasis is in the development and market introduction of XGEL™ oral delivery systems. These systems will replace current delivery modalities based on gelatin such as soft and hard capsules as well as gelatin-enrobed dosage forms. The XGEL™ film technology has significant potential to replace tablets, in particular coated tablets. Significant development and licensing Agreements have been executed with major pharmaceutical companies.

PharmaCore, Inc., High Point, NC

President and Chief Executive Officer (October, 2000 – July, 2001)
PharmaCore is a start-up venture focusing on the development, manufacturing and distribution of novel chemical building blocks for drug discovery in the pharmaceutical, agrochemical and biotechnology industries. Technology is based on novel synthetic methods leading to heretofore unavailable amino acid building blocks. In addition, to offering a portfolio of novel compounds, PharmaCore offers custom synthesis services for drug and bulk intermediates. Clients include several major drug companies interested in diversifying their compound libraries using unique building blocks.

LDS Technologies, Inc., Boothwyn, PA

Chief Operating Officer (May, 1999 – August, 2000)
LDS's technology and patent portfolio was acquired by a large European drug delivery company in August 2000. A 6-month consulting contract was executed with the acquiring company in order to assist in the transfer and further development of the technology. The (LDS) company had significant proprietary formulation expertise in microemulsions for oral, parenteral and pulmonary delivery of drug products. Responsibility included all phases of development to include formulation, analytical, stability, quality, compliance, regulatory affairs and manufacturing of clinical supplies. A sister company, AquaCap Pharmaceuticals, Inc. was established in order manufacture liquid-filled two piece hard gelatin and HPMC capsules using LDS drug delivery technology.

Banner Pharmacaps Inc., High Point, NC

Senior Vice President, Research and Development (January, 1996 – April, 1999); Corporate Vice President, Research and Development (June, 1994 - December, 1995). Directed all research and development activities for the softgel and Soflet® dosage forms including a pilot manufacturing facility capable of full-scale manufacturing. The product line included prescription

and OTC drug products as well as nutritional, cosmetic and recreational products.

Chase Pharmaceutical Company, Newark, NJ

Senior Vice President and Chief Scientific Officer, Quality Assurance and Scientific Affairs (October, 1992 - May, 1994); Vice President, Quality Assurance and Scientific Affairs (March, 1992 - September, 1992). Chase Pharmaceutical Company was acquired in March, 1994 by Sobel N.V. (Netherlands), the parent company of Banner Pharmacaps. Responsibility for all product development activities, quality assurance/control and regulatory affairs. Total staff of about 50 with 6 direct reports. The company was engaged in the manufacture of generic prescription and OTC drug preparations, nutritional supplements and contract manufacturing for the same preparations.

Schering-Plough Corporation, Kenilworth, NJ & Miami, FL

Director, Physical and Analytical Chemistry R&D (May, 1989 - March, 1992)
Responsibility for all physical and analytical chemistry studies in support of the development of transdermal and solid dosage forms (immediate and extended release delivery). The department was reorganized at my direction into support sections based on product lines to achieve significant integration of the formulation and analytical sciences. Total staff of 25 with two section leaders and an administration section for stability and facilities coordination.

Marion Laboratories, Inc., Kansas City, MO

Manager, QA Technical Services (July, 1987 - May, 1989)
Responsibilities included directing the activities of three quality sections: Raw Materials, Stability and Technical Services. Raw materials testing and release, finished diagnostic products testing and release, marketed product stability assessment, and laboratory technical services were primary responsibilities. Technical Services included production chemistry troubleshooting, analytical methods troubleshooting and improvement, and interaction with R&D laboratories to include technology transfer. Total staff of 23 including two supervisors.
Analytical Chemist, R&D Analytical Research Section (Mar., 1985 - June, 1987) Responsibilities included methods development for bulk drugs and finished products, pre-formulation studies, special chemical/physical studies in support of development and submissions, project team representation for chemistry aspects of drug development.

The Drackett Company (div. of Bristol-Myers), Cincinnati, OH

Scientist & Head, Emerging Technologies Group (March, 1984 - February, 1985)
Start-up group to evaluate new technologies as they may apply toward the development of new household products. Full supervisory and fiscal responsibility with a staff of three chemists.
Scientist & Head, Analytical Research and Services (February, 1982 - February, 1984)
Full supervisory and fiscal responsibility for a staff of seven including 4 chemists and 3 technicians engaged in analytical methods development, competitive product analysis, and analytical support for Product Development and Quality Control. Scientist, Analytical Research & Services (June, 1981 - January, 1982) Senior Research Chemist, Analytical Research & Services (December, 1978 - May, 1981) Technical assignments centered on analytical methods

development for product and process control, stability assessment and competitive product analysis.

BOARD MEMBERSHIPS

BioProgress Technology International, Inc., Atlanta, GA & March, United Kingdom

Executive Director (September, 2002 – January, 2003)
Non-executive Director & Consultant (July, 2001 – August, 2002)

ADDITIONAL TRAINING

Continuing education and training courses include short courses covering biopharmaceutics, transcutaneous drug delivery, statistics, stability, and instrumentation operation.

MANAGEMENT TRAINING

Internal and external courses covering management topics such as influence and interaction management, interviewing skills, time management, fast cycle time and managing personnel diversity represent continuing training in leadership skills.

MILITARY

Captain, USAR; Honorable Discharge, 1983. Military Intelligence Officer's Basic Course, 1974

PROFESSIONAL AFFILIATIONS

American Chemical Society
American Association of Pharmaceutical Scientists

PUBLICATIONS AND PATENTS

"Hydroxylagopodin B, A Sesquiterpenoid Quinone From A Mutant Strain of Coprinus macrorhizus microsporus," Carey B. Bottom and Donald J. Siehr (1975), Phytochemistry, 14, 1433.

"The Interference of Elemental Sulfur in the Determination of Trace Organics in Drinking Water by the Carbon Adsorption Method," Carey B. Bottom, Gary C. Magruder, Donald J. Siehr, Sotirios Grigoropoulos, and William P. Clarke (1976), Journal of Environmental Science and Health, A11, 409-415.

"Mechanism of the Ninhydrin Reaction," Carey B. Bottom, Samir B. Hanna, and Donald J. Siehr (1978), Biochemical Education, 6, 4-5.

"Structure of an Alkali-soluble Polysaccharide from the Hyphal Wall of the Basidiomycete, Coprinus macrorhizus microsporus," Carey B. Bottom and Donald J. Siehr (1979), Carbohydrate Research, 77, 169-181.

"Structure and Composition of the Alkali-insoluble Cell Wall Fraction of Coprinus macrorhizus var. microsporus," Carey B. Bottom and Donald J. Siehr (1980), Canadian Journal of Biochemistry, 58, 147-153.

"Toilet Cleaning Article and Method for Codispensing Disinfectant and Dye Having Resistance to Spectral Degradation," Carey B. Bottom, Jane F. Gilmore, and John L. Martin, Jr. (July 1, 1986), US Patent 4,597,941.

"Cleaning Composition and Its Method of Use," Richard S. Hutchings and Carey B. Bottom (November 29, 1988), US Patent 4,787,984.

"In-tank Toilet Dispenser," Richard S. Hutchings and Carey B. Bottom (February 13, 1990), US Patent 4,899,398.

"Stable Liquid Form of 5-Aminosalicylic Acid," Carey B. Bottom and Margaret N. Kwoka (April 23, 1991), US Patent 5,010,069.

"Immobilized Artificial Membrane Chromatography: Prediction of Drug Transport Across Biological Barriers," Francisco M. Alvarez, Carey B. Bottom, Prashant Chikale and Charles Pidgeon (1993), A Chapter in "Molecular Interactions in Bioseparation," Plenum Press.

"Dissolution Testing of Soft Shell Capsules-Acetaminophen and Nifedipine," Carey B. Bottom, Marijo Clark, and J.T. Carstensen (1997), Journal of Pharmaceutical Science, 86, 1056-1061.

"The Effect of Gelatin Cross-Linking on the Bioequivalence of Hard and Soft Gelatin Acetaminophen Capsules," Marvin C. Meyer, Arthur B. Straughn, Ramakant M. Mhatre, Ajaz Hussain, Vinod Shah, Carey B. Bottom, Ewart T. Cole, Larry L. Lesko, Henry Mallinowski, and Roger L. Williams (2000), Pharmaceutical Research, 17(8), 962-966.

"Hard Gelatin and Hypromellose(HPMC) Capsules: Estimation of Rupture Time by Real-time Dissolution Spectroscopy," Yasser El-Malah, Sami Nazzal, and Carey B. Bottom (2007), Drug Development and Industrial Pharmacy, 33(1), 27-34.

APPENDIX B

I. A multi-compartment capsule comprising:

a first receiving chamber comprising at least one ingredient having a first physical state, wherein said ingredient is selected from the group consisting of a nutraceutical, a vitamin, a dietary supplement and a mineral; and

a second receiving chamber comprising at least one ingredient having a second physical state, wherein said ingredient is selected from the group consisting of a nutraceutical, a vitamin, a dietary supplement and a mineral,

wherein (A) said first physical state of said ingredient of said first receiving chamber is different from said second physical state of said ingredient of said second receiving chamber and (B) said ingredient of said first receiving chamber is different from said ingredient of said second receiving chamber, and

wherein the multi-compartment capsule is a hard shell capsule.

II. A multi-compartment capsule, comprising:

a first receiving chamber comprising at least one active ingredient having a first physical state; and

a second receiving chamber comprising at least one active ingredient having a second physical state, wherein said first physical state of said active ingredient of said first receiving chamber is different from said second physical state of said active ingredient of said second receiving chamber,

wherein (A) said active ingredient of said first receiving chamber is different from said active ingredient of said second receiving chamber and not present in said second receiving chamber, and (B) the multi-compartment capsule is a hard shell capsule.